Complete Summary

GUIDELINE TITLE

United Kingdom national guideline on the management of the viral hepatitides A, B, and C 2008.

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. United Kingdom national guideline on the management of the viral hepatitides A, B & C 2008. London (UK): British Association for Sexual Health and HIV (BASHH); 2008. 27 p. [191 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: United Kingdom national guideline on the management of the viral hepatitides A, B & C. London (England): British Association for Sexual Health and HIV (BASHH); 2005. 22 p.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Viral hepatitides A, B, and C (hepatitis A, hepatitis B, hepatitis C)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention

Screening
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Nurses
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To offer recommendations on the diagnostic tests, treatment regimen and health promotion principles needed for the effective management of hepatitis A, B and C
- To reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection

TARGET POPULATION

Patients (primarily those aged 16 and older) in the United Kingdom with hepatitis A, hepatitis B, and/or hepatitis C

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

Hepatitis A Virus (HAV)

1. Assessment of clinical features
2. Serology: serum HAV-specific immunoglobulin M (IgM)
3. Other diagnostic tests
    - Serum/plasma aminotransferases (AST/ALT)
    - Bilirubin
    - Alkaline phosphatase levels
    - Prothrombin time (PT)

Hepatitis B Virus (HBV)

1. Assessment of clinical features
2. Hepatitis B serology

- HBV surface antigen (HBsAg)
- HBV "e" antigen (HBeAg)
- IgM anti-core antibody
- Immunoglobulin G (IgG) anti-core antibody
- HBV deoxyribonucleic acid (DNA)
- Antibody to hepatitis B e antigen (anti-HBe)
- Antibody to hepatitis B surface antigen (anti-HBs)
- Antibody to hepatitis B core antigen (anti-HBc)

3. Other diagnostic tests
    - AST/ALT
    - Bilirubin
    - Alkaline phosphates levels
    - PT

Viral Hepatitis C

1. Assessment of clinical features
2. Serology
    - A screening antibody test: enzyme-linked immunosorbent assay (ELISA)
    - Reverse transcription-polymerase chain reaction (RT-PCR) assay for viral ribonucleic acid (RNA) (viral load test)
3. Other diagnostic tests
    - Acute infection, as for hepatitis A
    - Chronic infection, as for hepatitis B

Management/Treatment

HAV

1. General advice and patient education
2. Reporting requirement
3. Screening for other sexually transmitted infections in cases of sexually acquired hepatitis
4. Criteria for inpatient or outpatient treatment in acute icteric hepatitis
5. Considerations for pregnant and breastfeeding women
6. Management of sexual contacts and other contacts
    - Partner notification
    - Human normal immunoglobulin administration
    - Hepatitis A vaccine
7. Management in cases of human immunodeficiency virus (HIV) co-infection
8. Follow-up
9. Primary prevention: vaccination recommendations and education

HBV

1. General advice and patient education
2. Reporting requirement
3. Referral to hepatologist or experienced physician
4. Screening for other sexually transmitted diseases in cases thought to have been sexually acquired, injecting drug users (IDUs) or as otherwise appropriate

5. Liver biopsy for assessment of chronic disease
6. Non-invasive assessment of liver fibrosis (e.g., hepatic elastography [fibroscan])
7. Criteria for inpatient or outpatient treatment in acute icteric hepatitis (same as hepatitis A)
8. Pharmacotherapy for chronic infection (lamivudine, adefovir, alpha interferon, pegylated interferons, entecavir, tenofovir, telbivudine, and possibly, if approved, emtricitabine, clevudine, valtorcitabine)
9. Combination versus monotherapy, especially in HIV co-infected patients
10. Surveillance for hepatocellular carcinoma (HCC)
11. Considerations for pregnant and breastfeeding women, including prevention of vertical transmission
12. Management of sexual contacts and other contacts
    - Partner notification, contact tracing, screening, and education
    - Hepatitis B immunoglobulin
    - Accelerated course of recombinant vaccine
13. Follow-up
14. Screening using anti-HBc
15. Primary prevention activities, such as vaccination
16. Hepatitis D virus (HDV) testing

HCV

1. General advice and patient education
2. Reporting requirement
3. Referral to hepatologist of experienced physician
4. Screening for other sexually transmitted diseases
5. Liver biopsy for assessment of chronic disease
6. Non-invasive assessment of liver fibrosis (e.g., hepatic elastography [fibroscan])
7. Pharmacotherapy: pegylated interferon alpha plus ribavirin
8. Duration of therapy based on genotype
9. Vaccination against hepatitis A and B
10. Considerations for pregnant and breastfeeding women, including vertical transmission prevention
11. Management of sexual contacts and other contacts: partner notification and contact tracing
12. Follow-up
13. Screening and primary prevention
    - Testing for hepatitis C
    - Needle and syringe exchange schemes

MAJOR OUTCOMES CONSIDERED

- Rates of infection of viral hepatitis A, B, and C
- Response rates to therapy
- Morbidity and mortality due to viral hepatitis A, B, or C infection
- Rate of fulminant hepatic failure
- Changes in response rates and disease severity in patients co-infected with human immunodeficiency virus (HIV) or multiple hepatitis viruses

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Search Strategy

For each type of hepatitis, a Medline search was performed for the years 1966 to 2008 (Feb.) for hepatitis types A and B and 1990 to 2008 (Feb) for hepatitis C. From the Medical Subject Heading (MeSH) terms "hepatitis A," "hepatitis B," and "hepatitis C," the following sub-headings were used: Complications, Drug Therapy, Diagnosis, Epidemiology, Etiology, Mortality, Prevention and Control, Therapy, Transmission, Virology. The searches were limited to "human" for all searches. For Drug Therapy, Prevention & Control, and Therapy, searches were limited initially to "randomized controlled trials" but in the absence of enough publications this was changed to "controlled clinical trials," "clinical trials," or "reviews" in that order. For the sub-headings other than these three the search was limited to "reviews." Textword searches for "hepatitis A," hepatitis B," and "hepatitis C" were combined, as appropriate, with textword searches for " complication$," "diagnosis," "prevention," "transmission," "immunoglobulin," "vaccine," "non-response," "non-responders," "HIV," "randomized controlled trial".

Criteria for inclusion:

- Evidence from randomised controlled trials (RCTs) was used where possible, and failing that the studies using other rigorous scientific method.
- Recommendations were based on RCT or other scientific evidence and graded accordingly.
- No harms are anticipated.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials

Level	Type of Evidence
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

Grade	Recommendation
A (Evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Previous versions of the guideline have been reviewed by the Health Advisers professional association (SHASTD), the Medical Society for the Study of Venereal Diseases (MSSVD), Association for Genitourinary Medicine (AGUM) and Royal College of Physicians. All previous versions have also been on the MSSVD, AGUM and the British Association for Sexual Health and HIV (BASSH) websites since 1998, where comments were invited from website visitors.

Prior to publication, the final draft of the updated guideline was placed on the BASHH website, and copies circulated to the BASHH branch chairs, Genito-Urinary Nurses Association (GUNA), and Society of Sexual Health Advisors (SSHA) chairs for comment and peer review. After a period of three months any comments received were reviewed by the guideline authors and acted on appropriately before final authorisation by the Clinical Effectiveness Group (CEG) was given and publication was undertaken.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (**I-IV**) and grades of recommendation (**A-C**) are defined at the end of the "Major Recommendations" field.

Hepatitis A Virus Infection

Diagnosis (See also the National Guideline Clearinghouse (NGC) summaries of the British Association for Sexual Health and HIV [BASHH] Sexually Transmitted Infection Screening Guidelines.)

Serology

- Confirmed by a positive serum hepatitis A virus-specific immunoglobulin M (HAV-IgM) which remains positive for 6 months or more. Hepatitis A virus-immunoglobulin G (HAV-IgG) does not distinguish between current or past infection and may remain positive for life.

Other Tests

- Serum/plasma amino-transferases (AST/ALT) 500 to 10,000 IU/L. Bilirubin up to 500 micromoles/L. Alkaline phosphatase levels <2x the upper limit of normal, but higher if there is cholestasis.
- Prothrombin time (PT) prolongation by more than 5 seconds suggests developing hepatic decompensation.

Management

General Advice

- Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (**III, B**).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Hepatitis A is a notifiable disease.

Further Investigation

- Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate.

Acute Icteric Hepatitis

- Mild/moderate (80%) - manage as an outpatient emphasising rest and oral hydration (**III, B**).
- Severe attack with vomiting, dehydration, or signs of hepatic decompensation (change in conscious level or personality) - admit to hospital (**III, B**).

Pregnancy and Breastfeeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens.
- Breastfeeding can be continued and most children will have mild or asymptomatic infection (**IV, C**).

Sexual and Other Contacts

- Partner notification should be performed for at-risk homosexual contacts (oro/anal, digital/rectal, and penetrative anal sex) within the period 2 weeks before to 1 week after the onset of jaundice. This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination) to be contacted via the public health authorities (consultant in communicable disease control [CCDC] or equivalent). The CCDC has a duty of confidentiality to the index patient.
- Hepatitis A vaccine may be given up to 14 days after exposure providing exposure was within the infectious period of the source case (during the prodromal illness or first week of jaundice) (**Ib, A**).
- Human normal immunoglobulin (HNIG) 250 to 500 mg intramuscularly should be considered for patients at higher risk of complications (concurrent chronic hepatitis B or C, chronic liver disease, or age >50 years old) (**Ib, A**). HNIG that is effective against HAV is in short supply in the United Kingdom (UK) and can only be obtained from the Heath Protection Agency (England and Wales), Health Protection Scotland or the Northern Ireland Public Health Laboratory Belfast.

- HNIG works best if given in the first few days after first contact, with an efficacy of 90% and is unlikely to give any protection more than 2 weeks after first exposure, but may reduce disease severity if given up to 28 days after exposure.
- Patients are most infectious for 2 weeks before the jaundice (i.e., before the illness is recognised).
- Hepatitis A vaccine schedule: doses at 0 and 6 to 12 months, 95% protection for at least 10 years (**Ib, A**). Current advice is to revaccinate after 10 years (**IIb, B**); however, there is increasing evidence that vaccine-induced immunity may be $\geq$20 years and possibly lifelong, so no further booster doses may be needed after the primary course in immunocompetent patients.
- Human immunodeficiency virus (HIV)-positive patients respond (antibody production) in 46% to 88% but titres are lower than in HIV-negative individuals and correlate with CD4 count (**IIa, B**).
- If patients with a low CD4 count (<300 cells/mm^3) are vaccinated, they should be revaccinated if the CD4 count rises above 500/mm^3 as a result of highly active antiretroviral therapy (HAART) if the HAV IgG remains negative on retesting.
- There is a combined hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (**IIa, B**).
- If an outbreak is suspected or if the index case is a food handler, notify the local CCDC/public health department by telephone (**IV, C**).

Follow-up

- See at 1 or 2 weekly intervals until aminotransferase levels are normal (usually 4-12 weeks) (**IV, C**).
- Immunity is usually lifelong.

Primary Prevention

- Current evidence still suggests that most men who have sex with men are not at increased risk for hepatitis A infection and therefore universal vaccination in this group cannot be firmly recommended (**III, B**). However, many outbreaks have been reported amongst homosexual men in large cities and therefore clinics in these areas (e.g., central London) should offer vaccination, particularly when increased rates of infection have been recognised locally (**III, B**).
- Screening for preexisting hepatitis A exposure before vaccination has been found to be cost-effective (**III, B**).
- Injecting drug users and patients with chronic hepatitis C infection should also be vaccinated (**III, B**).
- Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure, and for people at risk in an outbreak (**Ib, A**).
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (**IV, C**).

Hepatitis B Virus Infection

Diagnosis) See also the NGC summary of the BASHH guideline, Sexually Transmitted Infection Screening and Testing Guidelines Hepatitis A, B and C.)

Table. Hepatitis B Serology

Stage of infection	Surface antigen (HBsAg)	"e" antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+*	+	+	-	-	↑↑↑
Acute (resolving)	+	-	+	+	-	+/-	-	↑↑
Chronic (immune tolerant)	+	+	-	+	++	-	-	N**
Chronic (immune active)	+	+	-	+	+	-	-	↑
Chronic (eAg Neg.)	+	-	-	+	+	+/-	-	↑
Chronic (inactive carrier)	+	-	-	+	-	+	-	N
Resolved (immune)	-	-	-	+	-	+/-	+/-	N
Successful vaccination	-	-	-	-	-	-	+	N

* In very early infection the IgM anti-core can be negative and by definition so can the IgG

**N=Normal

Abbreviations: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B "e" antigen'; N, normal

Other Tests

- Acute infection - see hepatitis A.
- Chronic infection - in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 IU/L) and in many the liver enzymes will be normal. Only in severe late stage liver disease does the liver enzymes and the liver function tests (LFTs) become grossly abnormal. Disease activity correlates with HBV-DNA levels and a level $>10^5$ copies/ml is regarded as significant (in terms of risk of progression to cirrhosis and hepatocellular carcinoma) and meriting consideration of therapy.

Management

General Advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact, until they have become non-infectious or their partners have been successfully vaccinated (see below) (**III, B**).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood (**IV, C**).
- Hepatitis B is a notifiable disease.

Further Investigations

- Screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (**IIb, B**).
- Other tests such as liver biopsy (for staging and grading of liver disease) should be performed by specialists in this field (**IV, C**).
- Noninvasive methods of assessing liver fibrosis such as hepatic elastography (e.g., fibroscan) may provide useful information to complement the liver biopsy.

Acute Icteric Hepatitis

- As for hepatitis A

Treatment of Chronic Infection

- Refer all HBsAg-positive patients to a hepatologist or physician experienced in the management of liver disease (**IV, C**).
- Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of liver disease (**IV, C**). The decision to treat depends on pattern of disease, HBV-DNA level, and presence or absence of significant necro-inflammation and hepatic fibrosis. HBV-DNA cut offs of 10^5 , 10^4 and 10^3 copies/ml, are often used for HBeAg-positive chronic hepatitis, HBeAg-negative chronic hepatitis and cirrhosis respectively.
- Patients should be considered for therapy with lamivudine, adefovir, tenofovir, telbivudine, entecavir (or combinations of nucleos[t]ide analogues) or pegylated interferon (**Ib, A**). Additional treatments that may soon be licensed in HBV monoinfection include emtricitabine (FTC) (**Ib, A**), clevudine (**II, B**) and valtorcitabine (**III, C**). Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer.
- All patients should have an HIV test prior to starting HBV therapy because of the different treatment strategies required and the significant risk of anti-retroviral-resistant HIV developing if lamivudine, tenofovir or entecavir are used as monotherapy (**Ib, A**).
- Lamivudine, emtricitabine and tenofovir will suppress hepatitis B viral replication during therapy of HIV (see also the British HIV association guidelines on the treatment of HIV/HBV co-infection), and may delay liver damage if given as part of triple antiretroviral therapy. (**Ib, A**).
- Lamivudine and emtricitabine should only be given to HIV-positive patients in combination with tenofovir as part of highly active antiretroviral therapy (HAART) because of the rapid high rate of resistance that occurs to these

drugs if given as the only HBV-active agent (**Ib, A**). Entecavir should not be used in HIV-positive patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation.
- Adefovir or telbivudine can be used alone in HIV-positive patients (**II, B**).
- Active surveillance of cirrhotic patients for hepato-cellular carcinoma (HCC) leads to earlier detection and better treatment outcomes.
- In the context of HBV, there is a high risk of HCC development in some groups of non-cirrhotic patients. This includes African patients over the age of 20, Asian males over 40, Asian females over 50, and patients with a family history of HCC. HBV-infected patients meeting these criteria should be offered HCC screening.
- Specific therapy otherwise may not indicated unless decompensated liver disease ensues (**IV, C**).

Pregnancy and Breastfeeding

- Vertical transmission (mother to infant) of infection occurs in 90% of pregnancies where the mother is hepatitis B e antigen positive and in about 10% of surface antigen positive, e antigen negative mothers. Most (>90%) of infected infants become chronic carriers.
- Infants born to infectious mothers are vaccinated from birth, usually in combination with hepatitis B specific immunoglobulin, 200 IU intramuscularly (**Ia, A**). This reduces vertical transmission by 90%.
- There is some evidence that treating the mother in the last month of pregnancy with lamivudine may further reduce the transmission rate if she is highly infectious (HBV-DNA $\geq 1.2 \times 10^9$ geq/mL) (**III, C**), but this needs to be further substantiated.
- Infected mothers should continue to breastfeed as there is no additional risk of transmission (**II, B**).
- Hepatitis B may exacerbate after the end of pregnancy.

Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (**IV, C**). The infectious period is from 2 weeks before the onset of jaundice until the patient becomes surface antigen negative. In cases of chronic infection, trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than 2 or 3 years. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (**IV, C**). For screening of other non-sexual partners who may be at risk, discuss with the CCDC or equivalent.
- Specific hepatitis B immunoglobulin 500 IU intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needle-stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than 7 days (**Ib, A**).
- An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7 and 21 days or 0,

1, 2 months with a booster at 12 months in either course) (**Ib, A**). Vaccination theoretically will provide some protection from disease when started up to 6 weeks after exposure.
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10 IU/L) (**Ib, A**).
- The ultra-rapid vaccination schedule (0, 7, 21 days) leads to an anti-HBs antibody response in only 80% of recipients 4-12 weeks after the third dose. This rises to 95% just prior to the 12 month booster dose. It would be prudent to offer booster vaccinations of up to three further doses to the 20% of sexual or household contacts without detectable antibodies 4-12 weeks after the primary course (**IV, C**), even though most would have eventually developed an antibody response.

Follow-up

- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after 6 months even if the LFT is normal.
- Chronic infection (HBeAg-positive or HBV-DNA $>10^5$ IU/mL): If untreated, patients should be regularly reviewed at intervals of 1 year or less, ideally by a physician with expertise in this disease (**IV, C**).
- Immunity after recovery from infection (surface antigen negative) is lifelong in over 90%.

Screening and Primary Prevention (See also the NGC summary of the BASHH guideline, Sexually Transmitted Infection Screening and Testing Guidelines Hepatitis A, B and C.)

- Hepatitis B testing in asymptomatic patients should be considered in men who have sex with men, sex workers (of either sex), intravenous drug users, HIV-positive patients, sexual assault victims, people from countries where hepatitis B is common (outside of Western Europe, North America and Australasia), needle-stick victims, and sexual partners of positive or high-risk patients (**IV, C**). If non-immune, consider vaccination (see below) (**Ib, A**). If found to be chronic carriers consider referral for therapy (**Ia, A**).
- The simplest initial screening test in someone who is unvaccinated or is of unknown infection status is anti-hepatitis B core antigen (anti-HBc), with the addition of other tests as necessary (**III, B**). Some also screen for HBsAg initially (**IV, C**). Measure anti-HBs in those who have been vaccinated (**Ib, A**).
- Lone anti-HBc-positives. Measure anti-HBs and anti-HBe in those who are anti-HBc-positive, HBsAg-negative. If anti-HBs-negative and anti-HBe-negative, the anti-HBc may be a false positive. A single hepatitis B vaccine dose will induce anti-HBs if there has been past natural HBV exposure (anamnestic response, measured 4 weeks after single dose of HBV vaccine). If anti-HBs is still negative after a single booster, regard as non-infectious and give a full course of vaccine (**III, B**).
- Vaccination should be offered to non-immune patients in most of the above groups (**Ib, A**). The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (**IV, C**).
- HIV-positive patients show a reduced response rate to the vaccine and become anti-HBs negative more quickly, although double dose vaccine

increases the response by 13% (**IIb, B**). Response correlates with CD4 count if not on anti-retroviral therapy (ART) but also with viral load and ART use. Offer a repeat course of three doses of vaccine, which may be double dose, for HIV-positive vaccine non-responders (**II, B**). Vaccine response will also improve if the CD4 count rises and if patients have an undetectable viral load on ART. If patients do not respond to 6 doses initially, repeat vaccination once the CD4 is above 500 cells/mm^3 and the viral load is undetectable (**II, B**).

- The vaccination schedules for both the monovalent and the combined hepatitis A+B vaccines are outlined in the table below. The ultra-rapid 0, 7, 21 day regimen offers the advantage of a higher uptake of the full course and more rapid development of early immunity. Test for response (anti-HBs $\geq$10 IU/L, ideally >100 IU/L) 4 to 12 weeks after the last dose (**Ib, A**). Only 80% of ultra-rapid vaccinees will have detectable anti-HBs antibodies at this stage (see "*Sexual and Other Contacts*" above). If someone is at high risk of acquiring infection and is in the 20% without an early antibody response, consider further booster doses (**II, B**). They usually respond to further doses (up to three injections), ideally as a repeat course (**Ib, A**) with response rates up to 100% (**Ib, A**). Alternatively, for those at lower risk, offer a booster at 12 months by which time 95% would be anti-HBs-positive.
- Pre-S-containing vaccines (currently unlicensed) are effective (**Ib, A**) and may also be used for conventional-vaccine non-responders when available (**IIa, B**). Vaccines with novel adjuvants (e.g. Fendrix ®) are effective for haemodialysis patients and others who haven't responded to conventional vaccine (**IIa, B**).
- It is probable that booster doses of vaccine are not required for at least 15 years in immunocompetent children and adults who have responded to an initial vaccine course (**III, B**) although in those vaccinated in infancy 10% will be non-immune and show no immunological memory after 18 years. HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when anti-HBs levels fall below 100 IU/L (**III, B**).
- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given four or more years later without the need to restart a three-dose course (**III, B**). One or two doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively.

Table. Vaccination Schedules for Hepatitis B Using Monovalent Vaccine or Combined A+B Vaccine

Vaccination Schedule	Advantages	Disadvantages
0, 7, 21 days, 12 months	• Rapid immunity • Short duration • High antibody titres at 12 and 13 months • Better uptake	• Little information on HIV or other immune-compromised patients • Low antibody titre in the first year (but current evidence suggests that protection is still adequate in the immune-competent)

Vaccination Schedule	Advantages	Disadvantages
0, 1, 2, 12 months	• Shorter time to early immunity than the 0, 1, 6 course • High antibody titres at 12 and 13 months	• Antibody titres lower than the 0, 1, 6 regimen in the first year
0, 1, 6 months	• Higher antibody titres at 7 months than the other two regimens, although this may not be clinically important • Long established regimen • Most researched in HIV	• Poor uptake of the 6 month dose in the clinical setting

Hepatitis D (Delta Virus Infection, HDV)

This is an incomplete ribonucleic acid (RNA) virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of injecting drug users (IVDUs) and their sexual partners but also in female sex workers, and sporadically in other groups (Cross et al., 2008). Suspect HDV in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive. There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis. Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test. Response to anti-viral therapy is poor. Refer to physician with experience in managing HBV/HDV coinfections for assessment and treatment (**IV, C**).

Hepatitis C Virus (HCV) Infection (See also the NGC summary of the BASHH guideline, Sexually Transmitted Infection Screening and Testing Guidelines Hepatitis A, B and C.)

Diagnosis

Serology

- A screening antibody test such as an enzyme-linked immunosorbent assay (ELISA) or other immunoassay is initially performed and reverse transcription-polymerase chain reaction (RT-PCR) for RNA is used to confirm infection. In HIV-positive patients with a low CD4 count (<200 cells/mm^3) the EIA may be negative and an RT-PCR may be needed for diagnosis. An antibody test may not become positive for 3 or more months after acute infection but a test for HCV-RNA will be positive after only 2 weeks. Chronic infection is confirmed if an HCV-RNA assay is positive 6 months after the first positive test. Patients with low-level viraemia may require HCV-RNA levels testing on two or more occasions to confirm infection. All patients being

considered for therapy should have a viral RNA test to confirm viraemia and genotype assay (see flow chart in original guideline document entitled "Flow chart for hepatitis C testing using an ELISA assay").

Other Tests

- Acute infection - as for hepatitis A
- Chronic infection - as for hepatitis B

Management

General Advice

- Patients should be told not to donate blood, semen, or organs and given advice on other routes of transmission (see below) (**III, B**).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Acute hepatitis C infection is a notifiable disease.
- Refer all HCV-positive patients to a liver specialist for consideration of treatment (**Ia, A**).

Further Investigations

As for hepatitis B. Noninvasive methods of assessing liver fibrosis such as hepatic elastography (e.g., fibroscan) may provide useful information to complement the liver biopsy.

Treatment

- Acute icteric hepatitis: Acute icteric hepatitis: There is firm evidence that high dose alpha interferon or pegylated interferon given during the acute phase will reduce the rate of chronicity to only 10% or less (**IIb, B**). Spontaneous resolution of acute hepatitis C is signified by a loss of HCVRNA within the first 2 months. Only those HCVRNA positive for more than two months need to be treated. There is firm evidence that high dose alpha interferon or pegylated interferon given during the acute phase will reduce the rate of chronicity to only 10% (**IIb, B**). Spontaneous resolution of acute hepatitis C is signified by a loss of HCV-RNA within the first 2 months. Only those HCV-RNA positive for more than 2 months need to be treated. Genotype 1 infections require 24 weeks therapy whereas other genotypes need only 12 weeks treatment. Otherwise manage as for hepatitis A.
- Chronic infection: Peginterferon alfa with ribavirin will abolish chronic infection in approximately 50% of patients and is the approved therapy of the National Institute for Health and Clinical Excellence (NICE) (**Ia, A**). Treatment should be for 14-24 weeks for patients with genotypes 2 or 3. Other genotypes should be treated for 12 weeks and treatment only continued if there has been a reduction in HCV viral load to 1% of the level at the start of treatment. Patients achieving this 2 $\log_{10}$ reduction should be treated for 24-72 weeks depending on how quickly the viral load becomes undetectable.

Patients are more likely to respond if they have less severe liver disease (low fibrosis index on liver biopsy), low serum HCV-RNA levels (<2 million RNA copies/mL), if they are infected with certain HCV sub-types (types 2 and 3), or if they become HCV-RNA negative in the serum within 12 weeks (**Ib, A**).
- HIV-positive patients respond to treatment, although not as well as HIV-negative patients, and should be considered for therapy (**Ib, A**). Sustained virological response in those completing therapy is 11-29% for genotypes 1/4 and 43–73% for genotypes 2/3 (**Ib, A**).
- Patient selection for therapy depends on HCV genotype and viral load although a liver biopsy is not always necessary for making treatment decisions.
- Given the potential for fulminant hepatitis in co-infection hepatitis A and C and the worse prognosis of hepatitis B and C co-infection, patients with hepatitis C should be vaccinated against hepatitis A and B (**III, B**).

Pregnancy and Breastfeeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see "Transmission" section in original guideline document) (**II, B**).
- Breastfeeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load (**III, B**)

Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (**IV, C**). The infectious period is from 2 weeks before the onset of jaundice in acute infection. If there was no acute infection, trace back to the likely time of infection (e.g., blood transfusion, first needle sharing) although this may be impractical for periods longer than 2 or 3 years. Consider testing children born to infectious women (**IV, C**). For other non-sexual contacts thought to be at risk, discuss with the CCDC or equivalent.
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rate of transmission outside of HIV co-infection (see above), monogamous partners may choose not to use them (**IV, C**).

Follow-up

- As for hepatitis B (**IV, C**)
- Immunity is probably sub-type specific only - there are at least seven sub-types and reinfection/dual infection is well documented.

Screening and Primary Prevention

- Consider testing for hepatitis C in all IDUs, especially if equipment has been shared, in hemophiliacs or other patients who received blood or blood products pre-1990, and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown (**III, B**). Other groups to be considered for testing are sexual partners of HCV positive individuals, men who have sex with men (MSM), all HIV-positive patients, female sex workers, tattoo recipients, alcoholics, and ex-prisoners (**III, B**). It may take 3 months or more for the anti-HCV test to become positive after exposure (see "Incubation period" in the original guideline document).
- Since 1990 all donated blood in the UK has been screened for HCV and all blood products rendered incapable of transmitting infection (**III, B**).
- Needle and syringe exchange schemes have led to a fall in parenterally transmitted infections including HCV, HBV and HIV, although not consistently (**III, B**).

Levels of Evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of Recommendation

Grade	Recommendation
A (Evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

The original guideline document contains the following clinical algorithms:

- Hepatitis B screening using serum antibody to hepatitis B core antigen (anti-HBc)
- Hepatitis B screening using serum hepatitis B surface antigen (HBsAg)
- Hepatitis C testing using an enzyme-linked immunosorbent assay (ELISA)

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, management and treatment of patients who have viral hepatitides A, B, or C

POTENTIAL HARMS

- There is a significant risk of anti-retroviral-resistant human immunodeficiency virus (HIV) developing if lamivudine, tenofovir or entecavir are used as monotherapy in HIV and hepatitis B virus (HBV) co-infected patients.
- Lamivudine and emtricitabine should only be given to HIV-positive patients in combination with tenofovir as part of highly active anti-retroviral therapy (HAART) because of the rapid high rate of resistance that occurs to these drugs if given as the only HBV-active agent.
- Entecavir should not be used in HIV-positive patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.
- All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. United Kingdom national guideline on the management of the viral hepatitides A, B & C 2008. London (UK): British Association for Sexual Health and HIV (BASHH); 2008. 27 p. [191 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2008)

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

This guideline was commissioned and edited by the CEG of the BASHH, without external funding being sought or obtained.

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

GB: Speaker at an event funded by Roche. Researcher in Gilead-funded trials. Travel bursary from BMS.

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SB: Speakers bureau: BMS, Gilead, Roche, Schering Plough Travel bursary: Gilead, Roche, Tibotec

Research grants: Gilead, Roche Advisor: BMS, Roche, Schering Plough

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: United Kingdom national guideline on the management of the viral hepatitides A, B & C. London (England): British Association for Sexual Health and HIV (BASHH); 2005. 22 p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the British Association for Sexual Health and HIV Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Specifications for the development of UK guidelines on the management of sexually transmitted infections (STIs) and closely related conditions 2005. London (UK): British Association of Sexual Health and HIV (BASHH); 2005. 14

p. Electronic copies: Available in Portable Document Format (PDF) from the British Association for Sexual Health and HIV Web site.

Additionally, auditable outcome measures can be found in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated again on August 5, 2002. This summary was updated on November 27, 2002. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This NGC summary was updated by ECRI on November 1, 2005. The updated information was verified by the guideline developer on January 19, 2006. This summary was updated by ECRI on April 16, 2007, following the U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated by ECRI Institute on September 5, 2007, following the revised U.S. Food and Drug Administration advisory on Baraclude (entecavir). This NGC summary was updated by ECRI Institute on May 15, 2009.

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